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# Osteoporosis: Mechanism, Molecular Target, and Current Status on Drug Development

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## Abstract

Osteoporosis is a pathological loss of bone mass due to an imbalance in bone remodeling where osteoclast-mediated bone resorption exceeds osteoblast-mediated bone formation resulting in skeletal fragility and fractures. Anti-resorptive agents, such as bisphosphonates and SERMs, and anabolic drugs that stimulate bone formation, including PTH analogues and sclerostin inhibitors, are current treatments for osteoporosis. Despite their efficacy, severe side effects and loss of potency may limit the long term usage of a single drug. Sequential and combinational use of current drugs, such as switching from an anabolic to an anti-resorptive agent, may provide an alternative approach. Moreover, there are novel drugs being developed against emerging new targets such as Cathepsin K and 17β-HSD2 that may have less side effects. This review will summarize the molecular mechanisms of osteoporosis, current drugs for osteoporosis treatment, and new drug development strategies.

### Keywords

Osteoporosis; bone remodeling; osteoclasts; osteoblasts; osteocytes; antiresorptive drugs; anabolic drugs

## 1. INTRODUCTION

Osteoporosis (OP) is a skeletal disease characterized by decreased bone density and bone quality, increased skeletal fragility and fractures [1-3]. It is estimated that 33% of women

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and 20% of men are at risk for developing an osteoporotic fracture, particularly in the hip, spine and forearm [2, 4]. Thus, OP is a major and costly health problem, with estimated expenditures of €31 billion and $13.7–20.3 billion spent in the European Union and United States, respectively, for the treatment of osteoporosis-related fractures in 2010 [3, 5].

Osteoporosis represents a cumulative imbalance in bone remodeling [6], due to osteoclast reabsorption of bone in excess of osteoblasts production of mineralized extracellular matrix to rebuild the resorptive cavity [6-9]. Abnormal remodeling can affect both trabecular and cortical bone. Loss of trabecular bone leads to spinal and hip fractures, and cortical bone leads to long bone fractures.

Many risk factors are linked to OP. Sex hormones, genetically determined peak bone mass and family history, ageing, ethnicity, diet (low calcium and vitamin D intake), hyperthyroidism, Cushing's disease, anorexia nervosa, lifestyle (sedentary, cigarette smoking, excessive alcohol intake, certain medication use (glucocorticoids and some anticonvulsants), obesity, and disuse/ microgravity conditions (space flight, bed rest, paralysis) are common risk factors for the development of OP [10-15].

OP is classified into high turnover Type1 and low-turnover Type II osteoporosis. The risk of developing type I high turnover OP is greater in women [16] caused by low estrogen levels and increased bone resorption after menopause [6, 16-18]. In contrast, type II osteoporosis, also called senile osteoporosis, occurs in both men and women and is characterized by decreased osteoblast (Ob)-mediated bone formation (Ob-BF), increased marrow adipose tissue (MAT), and decreased bone remodeling [19-21].

Bone modeling, which shapes bone during development and affects periosteal bone formation, is a process where osteoclasts and osteoblasts work independently [22]. This process is thought to be irrelevant to osteoporosis, however, recent studies show that several approved drugs may work on modeling-based bone formation, present on the periosteum [22, 23].

Nutrient and environmental factors can impact bone mass. Calcium and vitamin D intake are required nutrients for bone health and the first choice in preventing and treating osteoporosis [24-26]. In addition, weight loss and daily exercise can reverse osteoporosis [27].

Pharmacological treatments, however, are necessary to improve bone mass and reduce fracture risks. Drugs for treating osteoporosis are categorized into either anti-resorptive drugs or anabolic drugs. Anti-resorptive drugs are more widely used than anabolic drugs. Six antiresorptive agents are now in clinical use [28]: 1) bisphosphonates, which are the first line drugs in treating osteoporosis and mainly work by directly inducing osteoclasts apoptosis [29]; 2) estrogen for estrogen replacement therapy [30]; 3) selective estrogen receptor modulators (SERM), which are designed to minimize the adverse effects of estrogen [31]; 4) denosumab, which inhibits receptor activator of NF-κB ligand (RANKL) [32]; 5) eldecalcitol (1α, 25-dihydroxy-2β-[3-hydroxypropyloxy] vitamin D3), a vitamin D analogue with strong inhibitory effect on bone resorption [33-35]; and 6) calcitonin, a second line method to inhibit osteoclasts [36]. Anabolic therapies include parathyroid hormone (PTH) analogues and romosozumab (an inhibitor of sclerostin) [28, 37].

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Despite the abundance of currently available drugs to prevent fractures, many patients are not being adequately treated for osteoporosis. This is primarily due to the difficulty of sustaining long-term compliance (40% of patients are still taking them after 1 year) and the perception of side effects (osteonecrosis of the jaw and atypical fractures), which has led to a decline in bisphosphonate of approximately 50% from 2008 to 2012 [32, 38].

This article will review the cellular and molecular mechanisms of OP, currently approved drugs for OP treatment, and new drug development strategies in treating osteoporosis.

## 2. CELLULAR AND MOLECULAR MECHANISMS

### 2.1. Process of Bone Remodeling

In general, bone remodeling can be separated into 5 phases: (1) Activation phase in which bone remodeling is initiated by either local mechanical or hormonal signal; osteocytes are believed to sense and transduce these signals into a biological response in bone [39-41]. In the activation phase, local [*i.e.,* TGF-β, macrophage colony-stimulating factor (M-CSF), receptor activator of NF-κB ligand (RANKL)] and systemic regulators [*i.e.,* vitamin D, calcium, PTH, estrogen, androgen, and glucocorticoid) will promote osteoclastogenesis and a new round of remodeling is commenced. (2) Resorption phase in which mature osteoclasts will secrete matrix metalloproteinases (MMPs) to digest both mineral and organic matrix. In this phase, the Howship's resorption lacunae are formed underneath the canopy cells [42, 43]. (3) Reversal phase in which the mature osteoclasts will undergo apoptosis and osteoblasts are directed to the resorption site [8]. In this phase, local molecules such as TGF-β will be released and attract osteoblasts to initiate bone formation [44, 45]. (4) Formation phase in which osteoblasts will take over the bone remodeling process, this process normally takes 4-6 months [41]. In this phase, many local and systemic regulators such as Wnt, Sclerostin, and PTH will induce osteoblastogenesis in bone [8]. Organic bone matrix (osteoid) composed of different proteins such as type I collagen starts to deposit until the entire compensation for bone resorption is achieved. (5) Termination phase in which an equal amount of bone matrix being resorbed and formed, the formation phase will be terminated. In this phase, osteoblasts will either go apoptosis or form the new osteocytes [8, 41], and bone mineralization will start and complete during this phase [46-48].

### 2.2. Cells Participate in Bone Remodeling

**2.2.1. Osteoclast—**To achieve their full function, differentiation and maturation are required for osteoclasts from osteoclast progenitors. This process starts with hematopoietic stem cells, which are the ancestors of all hematopoietic lineage cells. Hematopoietic stem cells hold the ability of self-renewal until they differentiate into multipotent progenitors [43]. These progenitors are still pluripotent, and to commit to osteoclast lineage, the expression of PU.1 will be upregulated. PU.1 is essential for the expression of several other proteins, which is required for osteoclastogenesis as the binding of which to their gene promoter is needed. c-fms, the receptor of M-CSF, is one of them, and the expression of which is a mark of the formation of osteoclast precursors [43, 49]. Binding of M-CSF to c-fms will result in an upregulation of the transcription factor c-FOS, which will lead to the expression of RANK, the receptor of RANKL, by accompanying with several other factors including PU.1

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and microphthalmia-induced transcription factor (MITF), another factor that is activated by M-CSF signaling [50]. The expression of RANK characterizes the late stage of osteoclast precursors that are ready to differentiate into osteoclasts [51]. Under basal conditions, RANK couples with TNF receptor-activating factors (TRAFs), specifically TRAF 1, 2, 3, 5, 6, and continually polyubiquitinates NF-κB-inducing kinase (NIK), which leads to its degradation [51]. Upon binding, RANK will release NIK, making it accumulate in the cytosol. NIK will then phosphorylate and activate the IKK complex in the canonical pathway. IKK complex is able to phosphorylate IκB, the suppressor of NF-κB, inducing its ubiquitination and degradation. Activated NF-κB will then recruit NFATc2, together with several other factors, and bind to the promoter region of NFATc1, known as the master transcription factor of osteoclastogenesis [43, 52, 53]. NFATc1 will then undergo autoamplification, and subsequently activate other osteoclastogenesis related genes together with PU.1 and MITF [54]. The last step of osteoclastogenesis is cell fusion, the exact mechanism is yet to be known though several factors such as OC-STAMP and DC-STAMP regulated by RANKL signaling pathway are thought to be essential [43, 55].

Two signaling systems, namely M-CSF/c-fms system and RANKL/RANK/OPG system, play a critical role in regulating osteoclasts. M-CSF is also an important factor for the survival of osteoclasts. M-CSF pathway can also activate Bcl-2, an essential factor for cell apoptosis prevention [56]. RANKL/RANK/OPG system is a major determinant of osteoclast activity. RANKL is a homotrimer transmembrane protein belonging to the TNF superfamily. It is present on the surface of several cell types, including osteoblasts and osteocytes, and can be cleaved by MMPs to produce a soluble form. The soluble form retains the ability to activate RANK [57, 58]. OPG is the decoy receptor of RANKL, and by competing with RANK, it can antagonize the activity of RANKL [59]. Denosumab, an antibody of RANKL, is shown to be effective in clinical trials and approved by the FDA that validates this pathway as a drug target [60].

**2.2.2. Osteoblast—**Targeting osteoblasts to stimulate bone formation in excess of bone resorption , unlike the success in inhibiting osteoclasts, is less well developed as a strategy to treat osteoporosis, though progress has been made. Mesenchymal stem cells (MSC), with the ability to differentiate into several other cell types such as adipocytes and chondrocytes, are thought to be the progenitor of osteoblasts. Three transcription factors, Runx2, Osterix (these two together are considered as master transcription factors) and β-catenin, are essential in the determination of osteoblast differentiation commitment of MSC, and loss of either one will result in complete absence of osteoblasts *in vivo* [61]. Runx2, together with its co-activator Cbtβ, will direct MSC differentiate into preosteoblasts. Osterix, the downstream regulator of Runx2, will then cooperate with Runx2 and further direct preosteoblasts differentiate into immature osteoblasts [61-63]. β-catenin is also a downstream factor of Runx2 and is able to enhance Runx2 expression by participating in the Wnt pathway [64-66]. The timing of Runx2 expression appears to be important. Runx2 expression reaches a peak in immature osteoblasts and drops in mature osteoblasts [67], and overexpression of type II Runx2 causes severe osteopenia due to the inhibition of osteoblasts maturation [68]. However, selective deletion of Runx2-II [69, 70] or conditional deletion of Runx2 [71] in differentiated osteoblasts causes osteopenia as well [72, 73]. Moreover,

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depending on the cell type, Runx2 may either enhance or reduce the expression of osteocalcin, which is a phenotypic marker of mature osteoblasts [61, 68, 74]. Runx2 may also inhibit the differentiation from osteoblasts to osteocytes, which indicates the dual function of Runx2 in osteoblasts differentiation [68]. So far, Runx2 pathways have not proven to be a therapeutic target, except for involvement in mechanosensing pathways.

Several pathways are regulating the differentiation of MSC. Among all of them, the Wnt pathway is the most important and well-established one controlling the formation of osteoblasts [75]. Wnt family contains 19 secreted glycoproteins, and they are indispensable for skeletal development, maintenance of bone homeostasis and bone remodeling [76-78]. In the canonical Wnt pathway, β-catenin will form a complex with axin and APC and undergo phosphorylation and degradation without Wnt ligands [79]. When Wnt ligands bind to the specific Frizzled receptor (FZD) and the coreceptors LRP5/6, they will free β-catenin from the complex and prevent its degradation [80]. Thus, β-catenin will then accumulate in the cells and translocate to the nuclei to regulate its target genes, including those encoding Runx2, osterix and OPG, whose expression will be increased,[9, 81]. It is also found that the Wnt pathway can inhibit the activity of PPAR-γ, a factor regulating the differentiation from MSC to adipocytes, which will, in turn, inhibit adipogenesis and enhance the differentiation from MSC to osteoblasts [82]. Though there are no Wnt agonists or biologics currently available, inhibiting sclerostin, an antagonist of the Wnt pathway, is effective in treating osteoporosis in clinical trials and thus marks the importance of this pathway in drug development [83].

**2.2.3. Osteocytes—**Osteocytes are the most abundant bone cells, and serve as a master regulator of bone remodeling [8, 84] by releasing hormones and sensing mechanical loading in bone [85, 86]. Osteocytes secrete several cytokines, including Dkk1 (an antagonist of Wnt pathway), sclerostin (Sost), RANKL, and OPG [7]. Mouse genetic studies have shown that conditional deletion of either Dkk1 and/or Sost from bone significantly increased bone mass [87-89]. The identity of the molecular targets that sense and transduce mechanical forces in bone likely includes polycystins and TAZ complex [90, 91], primary cilia [92-94], integrins [95], and hemichannels [96]. Theoretically, mechanical forces or administration of drugs that activate bone mechanosensors would be a novel treatment for osteoporotic disorders, particularly age-related osteoporosis and other bone loss caused by skeletal unloading [97].

## 3. CURRENT DRUGS (FIG. 1 AND TABLE 1)

### 3.1. Antiresorptive Drugs

**3.1.1. Bisphosphonates (Table 1)—**The coincidental discovery of bisphosphonates dates back to the 20$^{th}$ century, when pyrophosphate (PPi) was found to be a “water softener” generated *in vivo* that is capable of preventing the growth and dissolution of hydroxyapatite. At that time, researchers were focusing on the physical-chemical property of the bone. Considering their chemical properties, PPi and their stable organic analogues, bisphosphonates were tested for their antiresorptive potency. Several bisphosphonates were found extremely effective against bone resorption and not before long did the researchers find their mechanism of action is totally different from what they expected [98].

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The activity of bisphosphonates is first based on their extreme affinity to hydroxyapatite on bone surfaces. Besides the two phosphate groups on PPi, the hydroxyl group on the central carbon provides an additional anchor to the bone matrix, giving extra selectivity to the bone [99]. The other feature of bisphosphonates is their R group linking to the central carbon. Nitrogen containing R groups will give a 10 to 10,000 fold rise of antiresorptive activity to the bisphosphonates comparing to those without it, as a result of a totally different mechanism of action [29, 100]. Therefore, currently approved bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid) by the FDA for osteoporosis are all nitrogen containing and are used as first line drugs.

Nitrogen containing bisphosphonates can inhibit farnesyl pyrophosphate synthase, an indispensable enzyme for cell function and survival, leading to the apoptosis of osteoclasts [101]. The enzyme is universally present in all cells *in vivo*, so the selectivity of bisphosphonates is based on their extraordinary affinity to the bone surface, which gives them a half-life of at least 10 years according to an estimation [102]. The affinity also enables a “drug holiday” to patients taking bisphosphonates, which is a unique property among all drugs treating osteoporosis [103]. According to a study, no significant differences of key parameters of bone were found between patients taking alendronate for 10 years and those taking alendronate for 5 years with a subsequent 5-year drug holiday [104].

Despite the clinical effectiveness of bisphosphonates, several side-effects and concerns are limiting their clinical use. The most important one is osteonecrosis of the jaw (ONJ). Research reveals that approximately 94% of ONJ occurs in patients treated with a high dose of bisphosphonates for oncologic use [105]. However, for osteoporosis patients, this rate seems to be much lower (less than 1 in 10,000 cases comparing to 1 in 10 to 1 in 100 cases for oncology treatment) [106].

The compliance of patients is also a concern, as severe gastrointestinal problems may occur, and to alleviate the symptoms, patients need to fast overnight before taking the pill and wait for another 30min, during which they must stay upright, before they can eat or drink. Another problem associated with oral dose is poor bioavailability due to the high hydrophilicity of the drugs [107]. To address these problems, IV dose may be used especially for those who cannot take these drugs orally. However, as the majority of bisphosphonates are eliminated unchanged through urine, for patients with impaired kidney function, the dose must be cautiously adjusted. Moreover, several rare side effects such as severe musculoskeletal pain and atrial fibrilla-tion are also associated with an IV dose of bisphosphonates, though the mechanisms under which are still unclear [29].

Finally, as bisphosphonates inhibit the activity of osteoclasts, through the coupling, it will also inhibit the activity of osteoblasts and, in turn, slow down bone turnover rate. Several concerns are raised that the decreased remodeling rate may cause increasing accumulation of micro-damage in bone, as originally discovered in dogs treated with bisphosphonates [108]. Atypical fractures of a long bone are now recognized as a complication of bisphosphonates that may reflect poor bone quality due to the suppression of bone turnover. This complication has led to shorter durations of therapy and treatment holidays, the use of agents with faster “off rates”. Atypical long bone fractures are found in patients with long term use

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of bisphosphonates, which may associate with decreased bone turnover rate, though the rate is relatively low comparing to the rate of fractures prevented by bisphosphonates [109]. Nevertheless, the effect and risk of bisphosphonates usage beyond 5 years are still obscure and further research is needed to determine the optimal time range for bisphosphonate treatment.

**3.1.2. Estrogen and SERMs (Table 1)—**Estrogen functions as an inhibitor of RANKL and an enhancer of OPG production by binding to the ERα receptor, mainly expressed in bone mass [110]. As an inhibitor of osteoclast activity, in normal conditions, estrogen will balance the bone remodeling process. However, after menopause, the production of estrogen will decrease, and the balance will be broken, as a result, significant bone loss will occur. As expected, estrogen replacement therapy is a direct solution to this issue, which has been employed, even since the 1980s [21]. However, long term treatment with estrogen is related to serious side effects such as breast cancer, deep vein thrombosis (DVT) and stroke [111]. To circumvent these defects, selective estrogen receptor modulators (SERMs) are introduced to maintain the benefits of estrogen while avoiding its side effects. Currently, only two SERMs are approved by the FDA for the treatment or prevention of osteoporosis: raloxifene, which was approved back in 1997, for the prevention and treatment of osteoporosis, and bazedoxifene, which was approved in 2013 and only in combined use with estrogen, for the prevention of osteoporosis.[6] Though potent in decreasing vertebral fracture risk, these drugs fail to show sufficient effect against hip or nonvertebral fractures. The elevated possibility of DVT, stroke and breast cancer occurrence remains to be a problem in prolonged use [6, 112]. Moreover, when discontinued, a rapid increase in the remodeling rate will take place, which will result in fast bone loss with a higher risk of fracture [113]. In conclusion, only relatively young patients with a high risk of vertebral fracture and neglectable risk of nonvertebral fracture and DVT are suitable for this treatment. The prolonged use of estrogen or SERMs should be avoided and when the treatment is discontinued, patients should switch to another drug immediately [32].

**3.1.3. Other Drugs (Table 1)—**Denosumab is the first drug designed to target fundamental biologic pathways in bone remodeling approved by the FDA in 2010 [6, 21]. Denosumab is a human IgG2 monoclonal antibody that binds to RANKL, preventing RANKL from activating its receptor (RANK) on the surface of osteoclasts. In clinical trials, higher bone mineral density (BMD) increase is observed in patients treated with denosumab than those treated with bisphosphonates [114]. However, unlike bisphosphonates, discontinuation of denosumab will initiate a tremendous increase in bone turnover rate starting within the first few months, leading to a higher risk of fracture [115]. Furthermore, in oncological use, denosumab related osteonecrosis of the jaw is observed [116]. As this drug is relatively new comparing with other first line drugs, more research on the adverse effect is needed for optimal use. Calcitonin, though effective, is hardly competent to other antiresorptive drugs. The increasing rate of cancer in long term treatment also limits its clinical use [21].

Eldecalcitol is an active form of vitamin D analogue that has been used for the treatment of osteoporosis for many years in Japan [33-35]. Eldecalcitol monotherapy is now going

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through clinical trials to treat glucocorticoid-induced osteoporosis compared with alfacalcidol monotherapy. Given the fact that the active analogues of vitamin D exert their pharmacological activities by mechanisms different from those of other current drugs, further studies will be needed to reveal the clinical potential of eldecalcitol either as monotherapy or combination therapy for osteoporosis.

## 3.2. Anabolic Drugs

**3.2.1. PTH Analogues (Table 1)—**From their mechanism of action, antiresorptive drugs cannot stimulate bone formation directly as their effects mainly base on the inhibition of osteoclast activity and the subsequent reduction of bone remodeling. Thus, when treating patients with severely damaged bone quality, antiresorptive drugs may not be the first ones to consider [23]. Anabolic drugs which act by stimulating bone formation may be a key to address this problem, and PTH analogues are currently the most widely used anabolic drugs.

PTH is a hormone secreted by parathyroid glands to increase the calcium level *in vivo.* To achieve this, PTH will accelerate the resorption of bone by enhancing osteoclast activity [117]. At first glance, PTH seems to worsen the condition of osteoporosis patients. However, researchers found that its activity of elevating bone remodeling only occurs when its receptor is activated continually. During intermittent and low dosed activation, the PTH receptor is able to increase bone formation. This two-sided effect is mainly due to the two different conformations of the PTH receptor: $R^0$ responsible for prolonged activation and RG for intermittent activation [118]. Two PTH analogues were approved by the FDA: teriparatide, a fragment of full-length PTH, in 2002 and abaloparatide, a PTH-related peptide (PTHrP), in 2017 [6, 23]. Abaloparatide seems to be more potent than teriparatide, which may base on its higher affinity to RG [119].

Despite their potency against both vertebral and non-vertebral fractures, increasing the risk of osteosarcoma is observed in rodents treated with an excessive dose of teriparatide [120]. Moreover, as the increase in osteoblast activity will enhance osteoclast activity through the coupling, together with the side effect of activating $R^0$, during prolonged use, an increase in resorption will occur [119]. Considering these problems, the use of PTH analogues is restricted to no more than 2 years, and during the discontinued period, as tremendous bone loss is observed, switching to other drugs in essential [121].

**3.2.2. Romosozumab (Table 1)—**Romosozumab is a monoclonal antibody of sclerostin [32] and has only recently approved by the FDA in April 2019. Several distinct pharmacological properties are observed during the research of romosozumab. To begin with, unlike PTH analogues, not only does romosozumab have the ability to enhance bone formation by upregulating the Wnt pathway, but it also holds the potency to reduce bone resorption as sclerostin is also an enhancer of RANKL synthesis [37, 122, 123]. Besides, different from any other osteoporosis drugs, the major effect of romosozumab is modeling, not remodeling based.[124] These unique features give romosozumab superior potency when used both alone or together with other drugs [37, 125]. However, the anabolic effect of romosozumab tends to wear off, though the antiresorptive effect persists [126]. Moreover, the power of romosozumab is likely to be restricted to preventing vertebral fractures [37],

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and the probability of increasing cardiovascular disease risk still requires more researches [125].

### 3.3. Combinational and Sequential Use of Drugs

Considering their different mechanism of action, the combinational use of antiresorptive and anabolic drugs was thought to be a more effective way to prevent and treat osteoporosis. Nevertheless, based on current clinical data, the synergetic effects are hardly obvious and are limited to certain combinations. Shen *et al.* reviewed several clinical studies regarding the combinational use of teriparatide with other antiresorptive drugs, and found that comparing with single drug treatment, only a small increase in bone density is observed, and the combination is restricted to teriparatide with estrogen/SERM and with denosumab. For other combinations, the effect is no better than the single drug [127]. As the other two anabolic drugs are relatively new, no clinical data of their combinational use is published.

As stated, prolonged use with a single osteoporosis drug should be avoided as it is related to several problems, such as severe side effects and wearing off of anti-osteoporosis potency. Thus, to circumvent the discontinuing effects, sequential treatment is the first thing to consider. In clinical practice, bisphosphonates have already been used after denosumab or estrogen/SERM discontinuation to prevent the rapid growth of the remodeling rate [32]. As for the transition between anabolic and antiresorptive drugs, the order is of vital importance. In a study regarding the sequential use of denosumab and teriparatide, the patients were randomized into three groups: a two-year teriparatide treatment followed by a two-year denosumab treatment, a two-year combinational treatment of both drugs switching to a two-year denosumab treatment and a sequential therapy from a two-year denosumab treatment to a two-year teriparatide treatment. BMD increase of different sites was examined at the end of the study, and researchers found that although no difference was shown in lumbar spine BMD (LSBMD) (18.3%, 16.0% and 14.0%, respectively), the first two groups showed a higher increase in femoral neck BMD (FNBMD) (8.3%, 9.1% and 4.9% respectively) and total hip BMD (THBMD) (6.6%, 8.6% and 2.8%) than the third group. A decrease of THBMD and FNBMD is even observed at the beginning of the switch in the third group [128]. The effectiveness of the transition from anabolic drugs to antiresorptive drugs is also confirmed by other studies, as the BMD increase in all of the following transitions: teriparatide to raloxifene, PTH to alendronate, abaloparatide to alendronate and romosozumab to denosumab beat their own controls: teriparatide to calcium and vitamin D, PTH to placebo, placebo to alendronate and placebo to romosozumab, respectively [37, 129-131].

## 4. DRUGS AND TARGETS UNDER INVESTIGATION (FIG. 1 AND TABLE 2)

### 4.1. Drugs in Clinical Trials

Despite the emerging drug targets, most drugs in clinical trials are still focusing on conventional targets. Encouraged by the success of romosozumab, more efforts are made on the research of sclerostin inhibitors, and two drugs are now fighting their way in clinical trials, hoping to be approved in the future. Blosozumab (LY 2541546), a sclerostin antibody structurally diverse from romosozumab, has shown to be potent in a phase II trial. Both

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spine and total hip BMD are statistically increased and are dose dependent. Although anti-blosozumab antibody is developed in some patients, especially in the lower dose groups, this seems to have negligible effects on the drug's activity. In addition, no severe side effects related to the treatment are observed[132]. A follow-up study also shows that after a year of drug discontinuation, the spine and total hip BMD in the treatment group, though decreased, are still higher than both baseline and those in the placebo group [133]. Together these results indicate blosozumab is a highly promising drug candidate. SHR-1222 is the newest monoclonal antibody targeting soluble sclerostin seeking to participate in clinical trials. No clinical data have been published at this point.

SERM is another important class of molecules in OP drug development (Table 2). Unfortunately, the only two SERM drugs, arzoxifene and lasofoxifene, failed in late clinical trials due to different reasons. According to a comparison study between arzoxifene and raloxifene, patients treated with arzoxifene have higher increases in lumbar spine, femoral neck and total hip BMD. Some side effects associated with raloxifene, especially hot flushes, are also less frequent in arzoxifene treatment group. Nevertheless, other side effects such as nasopharyngitis are increased and the BMD increase does not translate into less non-vertebral fracture frequency, which ultimately leads to its failure [139, 140]. Lasofoxifene, on the other hand, shows effectiveness in both preventing vertebral and non-vertebral fractures with a 0.5 mg daily dose. The risks of stroke, coronary heart disease and ER-positive breast cancer are also found to be decreased comparing to the placebo group[141], which leads to its approval in Europe. However, it failed to gain US FDA approval, as increasing risk of death is found in patients treated with a low dose of lasofoxifene in clinical trials. The developer decided to quit from seeking approval by the FDA [142]. Interestingly, the FDA has recently granted a fast track designation to lasofoxifene in treating breast cancer, which may help it finally finding its way to the US market for a different disease indication.

Though denosumab was approved back in 2010, only one RANKL antibody is now in clinical trials. TK006 (Table 2) is a full human monoclonal antibody of RANKL and just started its phase I clinical trial. Although no clinical results regarding osteoporosis are reported, when treating bone metastasis from breast cancer, some side effects, such as hypocalcemia, limbs pain and toothache, have been observed [143].

Calcium-sensing receptor (CASR) in parathyroid glands was once thought to be a promising target to treat osteoporosis. By blocking it, the secretion of PTH will be upregulated, and through activating PTH receptors on bone cells, similar effects with PTH analogues are expected to be seen [144]. Two drugs, Ronacaleret (SB-751689) and Encaleret (MK-5442), were once in clinical trials (Table 2). Nevertheless, far from developers' imagination, only moderate effect in increasing BMD was seen during the phase II trials of both candi-dates, which is no match for classical osteoporosis drugs such as alendronate. Both drugs were withdrawn from further development and this target is no longer thought to be valid [142]. Activation of CASR in osteoblasts is another potential way to stimulate bone formation, however, calcimimetics, which activate CASR, while effective in suppressing PTH from the parathyroid gland, have a little direct effect to increase bone mass, and are not used to treat

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OP [145]. Stron-tium ranelate, a second line treatment for OP in Europe, may function in part through the activation of CASR [146].

Cathepsin K is a novel target for antiresorptive drug development. It is a human protease and during bone remodeling, high levels of cathepsin K will be expressed in osteoclasts and secreted into BMU to break down type I collagen expressed in bone matrix and fa-cilitate the resorption process. In contrast, osteopetrosis (abnormally high BMD) is found in cathepsin K knock out mice [147, 148]. As the number of osteoclasts will be maintained during the treatment, coupled downregulation of osteoblasts is thought to be avoided with cathepsin K inhibitors. Following this concept, several drugs have been developed and reached clinical trials. Odanacatib (MK-0822) (Table 2) is one of the cathepsin K inhibitors and reached phase III clinical trials. During an 8-year Phase II study, patients treated with odanacatib have a continuous increase in BMD at multiple sites till year 5, and the BMD is then maintained or slightly increased. The bone turnover rate also decreases comparing with the baseline [149]. Another study suggests that the efficacy of odanacatib is equivalent to traditional bisphosphonates with little influence on bone formation [150]. However, an increasing risk of stroke is found in clinical studies and further development of the drug is halt by the developer [142]. Till now, whether this side effect, universally present in all cathepsin K inhibitors, is still obscure, further research on this topic is needed. Despite this, two other cathepsin K inhibitors: balicatib (AAE581) and ONO-5334, both in their phase II trials, are still under development. Balicatib shows the effects of enlarging osteoclasts and inhibits their abilities to degrade collagen [151], though it was found that Balicatib may cause morphea-like skin reactions [152]. For ONO-5334, increases of BMD at multiple sites and decreases of bone resorption markers, which are comparable to alendronate, are reported. Moreover, the suppression of bone formation markers is neglectable and no dose dependant severe side effects related to the drug are observed during the 1-year-trial [153]. Together these results grant ONO-5334 for further studies.

MK-0429 (Table 2) is an $\alpha_v\beta_3$ integrin inhibitor once developed for prostate cancer treatment. Considering the importance of the integrin, it is now also in phase I trial for the treatment of osteoporosis. There are some clinical data showing the ability of MK-0429 to increase lumbar spine BMD dose dependently. While the drug is well tolerated, the rate of headache is found to positively correlate with drug dosage, and the increase of BMD at hip sites can only be found at a higher dose [154].

### 4.2. Preclinical Drugs with Known Targets

c-fms, a receptor controlling another fundamental pathway of osteoclastogenesis, is also considered a possible target. However, despite so much effort being put on developing its inhibitors, with some drugs already in clinical trials, all of them are targeting other diseases such as cancer and rheumatoid arthritis, and no compounds treating osteoporosis have been published recently regarding this receptor [155].

Other than directly stimulating estrogen receptors by injecting estrogen or SERM, indirectly upregulating the concentration of estrogen specifically in bone by inhibiting 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD2) is also a possible way to treat osteoporosis. 17β-HSD2 is an enzyme responsible for converting the bioactive estradiol into

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the inactive estrone. As this enzyme is only concentrated in a small number of tissues other than bone with heart and breast, not in the list, the severe side effects such as increasing cardiovascular disease and breast cancer risks associated with estrogen/SERM may be avoided [156]. Numerous compounds have been developed to inhibit 17β-HSD2 (Table 2) in recent five years, and the $IC_{50}$ of some compounds is already in the sub-nanomolar range [134-137, 156]. Nevertheless, only the fracture healing model has been assessed *in vivo* [137]; more researches should be conducted on their antiresorptive efficacy in animal models.

Serotonin, or 5-HT, is a neurotransmitter and plays vital roles in regulating bone formation. While central synthesized serotonin functions as an enhancer of bone formation, peripheral derived one inhibits this process by impeding osteoblastogenesis [157]. Tryptophan hydroxylase 1 (Tph-1) is an enzyme mastering the synthesis and functions of peripheral synthesized serotonin, and an inhibitor of it; LP533401 (Table 2) shows promising effects in increasing bone mass in ovariectomized mice. Encouraged by these discoveries, Fu *et al.* developed a small molecule targeting Tph-1, which showed comparable efficacy with PTH in increasing BMD in ovariectomized mice [138]. Although further development is still needed, these findings together validate Tph-1 as an intriguing target for osteoporosis.

Mechanical force is another important regulator of bone formation, as higher BMD is seen in the arm being used for tennis playing than the other one in tennis players [158]. In contrast, as stated, immobilization is a common cause of osteoporosis. The complex formed by polycystin 1 (PC1), polycystin 2 (PC2) and TAZ is gradually established as the mechanosensor expressed on osteoblasts, and deletion of either PC1 or PC2 will result in osteopenia in mice [97]. Recently, the detailed mechanism of this process has been proposed by Xiao and his coworkers. They suppose that after sensing the mechanical signal, the C terminal of PC1 (PC1-CTT), together with TAZ, will be cleaved from the complex and translocate to the nucleus, where they will simultaneously induce Runx2-mediated downstream activation but inhibit PPARγ-mediated downstream transcription. Moreover, they indicate that by enhancing the interaction between PC1 and PC2, this cleavage will be facilitated, and as a proof of concept, a “molecular staple” (mechanomimetics) identified by virtue screening has been tested *in vitro* and *in vivo* where it shows promising effect in enhancing osteoblast-mediated bone formation [90]. Albeit further confirmation of the molecular mechanism of the compound is in demand, these findings still propose a brand-new osteoporosis target.

### 4.3. Other Drugs in Preclinical Stage

Considering the inconvenience of dose and price of antibodies, efforts have also been put in replacing them with small molecules, and RANKL is a hot target. Though several compounds have been made targeting RANKL and shown promising antiresorptive effects, their potency is still relatively low and further development is needed [159, 160]. Whole cell screening has helped Saito and his coworkers find a new compound in treating osteoporosis, but the potency is still very low and the target is unclear [161]. By combining the fragments of known anti-osteoporosis compounds, Zhao *et al.* found a potent compound both *in vitro* and *in vivo*, with the target still to be determined [162].

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## CONCLUSION

Tremendous progress has been made during the past few decades on the biology of bone metabolism. Except for several minor problems to address, the process of bone remodeling and osteoclast differentiation is well understood. However, the biology of os-teoblast, the communication between bone cells and the participation of other cells, especially immune cells, remain to be obscure. The bone modeling process is also overlooked in the study of osteoporosis, maybe because bone modeling is more prevalent at young ages and does not participate in bone metabolism much at the age when osteoporosis is likely to occur. Nevertheless, studies have found that nearly all anabolic drugs, including PTH analogues [163], work more or less on bone modeling. Thus, a thorough understanding of bone modeling is in demand for the development of better anti-osteoporosis drugs.

For current drugs, in spite of their potency, prolonged use is typically related to decreasing efficacy or severe side effects. As no drug is currently in phase III clinical trials, no better new drug can be expected to be approved in a short period of time. As a result, sequential and combinational use is the only way to address these problems currently. While before 2017, teriparatide is the only anabolic drug approved in the US, abaloparatide and romosozumab are available now, and their combinational and sequential use with anti-resorptive drugs should be studied to give patients better treatments.

Antiresorptive drugs are somewhat mature when looking at the efficacy and duration of bisphosphonates. However, to gain more BMD, anabolic drugs theoretically perform better than them. As the variety of available anabolic drugs is limited, with no small molecules in the list, more effort should be put in developing anabolic drugs, which is also welcomed by the emerging targets suitable for drug development.

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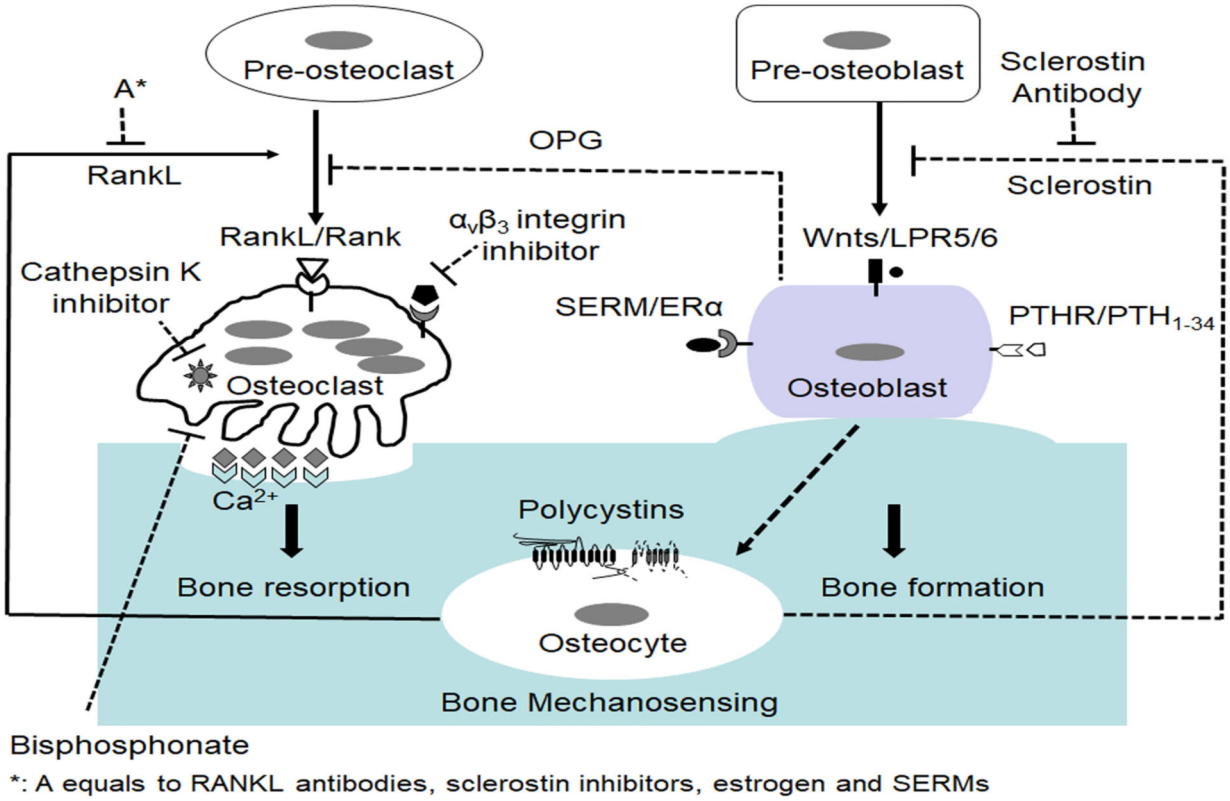


**Fig (1).**

Therapeutic targets for osteoporosis in bone remodeling. Cell lineage from pre-osteoclast to osteoclast will result in bone resorption and that from pre-osteoblast to osteoblast will result in bone formation. Osteoblast can further differentiate into osteocyte which can regulate both bone resorption and bone formation. RANKL antibodies, estrogen and SERMs, cathepsin K inhibitors, $\alpha_v\beta_3$ integrin inhibitors and bisphosphonates are all considered as antiresorptive drugs, while PTH analogues and sclerostin inhibitors are all considered anabolic drugs, though sclerostin inhibitors work both by inhibiting the functions of osteoclasts and promoting those of osteoblasts.

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**Table 1.**

FDA approved drugs for osteoporosis.

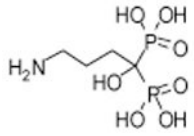
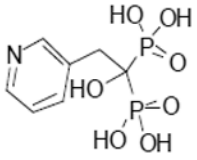
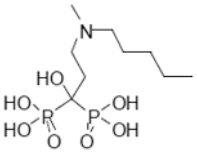
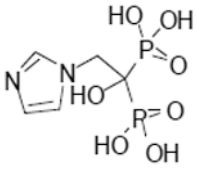
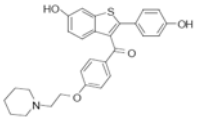
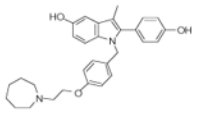
| Category | Drug name | Structure | Year Approved | Mechanism of Action |
|---|---|---|---|---|
| Bisphosphonates | Alendronate |  | 1995 | Antiresorptive action through direct inhibition of osteoclast activity |
| | Risedronate |  | 1998 | |
| | Ibandronate |  | 2003 | |
| | Zoledronic acid |  | 2003 | |
| SERMs | Raloxifene |  | 1997 | Antiresorptive action through inhibition of osteoclast activity by activation of ERα receptor and enhancement of OPG/RANKL ratio |
| | Bazedoxifene |  | 2013 | |
| RANKL inhibitors | Denosumab | Monoclonal antibody | 2010 | Antiresorptive action through inhibition of osteoclast activity by direct binding to RANKL |
| PTH analogues | Teriparatide | PTH (1-34) peptide | 2002 | Activation of osteoblast function by activation of PTH or PTHrP receptor |
| | Abaloparatide | PTHrP (1-34) peptide | 2017 | |
| Sclerostin inhibitors | Romosozumab | Monoclonal antibody | 2019 | Activation of osteoblast function by direct binding to Sclerostin |

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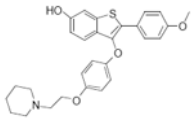
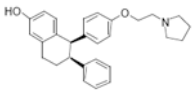
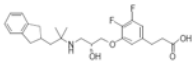
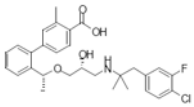
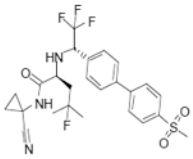
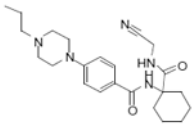
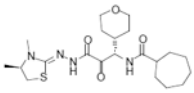
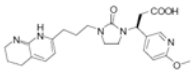
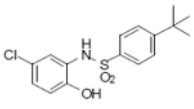
**Table 2.**

Drugs under development for osteoporosis with validated targets

| Category | Name | Structure | Status | Mechanism of Action |
|---|---|---|---|---|
| Sclerostin inhibitor | Blosozumab | Monoclonal antibody | Phase II Completed | Activation of osteoblast function by direct binding to Sclerostin |
| | SHR-1222 | Monoclonal antibody | Preparing for phase I | |
| SERMs | Arzoxifene |  | Reached phase III Failed due to low efficacy | Antiresorptive action through inhibition of osteoclast activity by activation of ERα receptor and enhancement of OPG/RANKL ratio |
| | Lasofoxifene |  | Reached phase III Approval withheld by FDA due to safety concerns | |
| RANKL inhibitor | TK006 | Monoclonal antibody | Phase I | Antiresorptive action through inhibition of osteoclast activity by direct binding to RANKL |
| Calcium-sensing receptor antagonist | Ronacaleret |  | Reached phase II Failed due to low efficacy | Blocking calcium-sensing receptor that stimulates PTH release from the parathyroid glands |
| | Encaleret |  | Reached phase II Failed due to low efficacy | |
| Cathepsin K inhibitor | Odanacatib |  | Reached phase III Failed due to safety issues | Inhibition of osteoclast activity by inhibition of Cathepsin K activity |
| | Balicatib |  | Phase II | |
| | ONO-5334 |  | Phase II | |
| αvβ3 integrin antagonist | MK-0429 |  | Phase I | Inhibition of osteoclast activity by selectively binding to αvβ3 integrin receptor |
| 17β-HSD2 inhibitors | 17[134] |  | Preclinical $IC_{50}$ = 0.80μM | Controlling the availability of biologically active estrogens and androgens in the tissues |

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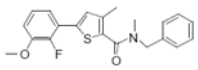
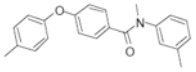
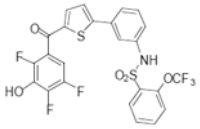
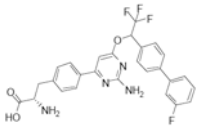
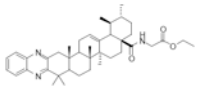
| Category | Name | Structure | Status | Mechanism of Action |
|---|---|---|---|---|
| | 21[135] |  | Preclinical $IC_{50}$ = 235nM | |
| | 4[136] |  | Preclinical $IC_{50}$ = 160nM | |
| | 15[137] |  | Preclinical $IC_{50}$ = 2.0nM | |
| TPH-1 inhibitor | LP 533401 |  | Preclinical $IC_{50}$ = 0.4μM | Inhibition of gut-derived serotonin synthesis and promotion of osteoblast function |
| | 9a[138] |  | Preclinical. $IC_{50}$ = 6.22μM | |